What is claimed is:

1. An antibody having a first antigen binding site specific for a first VEGF receptor and a second antigen binding site specific for a second VEGF receptor.

2. The antibody of Claim 1 wherein the first and second VEGF receptors are mammalian.

3. The antibody of Claim 1 wherein the first and second VEGF receptors are human.

4. The antibody of Claim 3 wherein the first and second VEGF receptors are selected from the group consisting of KDR, Flt-1 and Flt-4.

5. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the second VEGF receptor is Flt-1.

6. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the amino acid sequences of the complementarity determining regions (CDRs) of the first antigen binding site comprise:

SEQ ID NO: 1 at CDRH1;
SEQ ID NO: 2 at CDRH2;
SEQ ID NO: 3 at CDRH3;
SEQ ID NO: 4 at CDRL1;
SEQ ID NO: 5 at CDRL2; and
SEQ ID NO: 6 at CDRL3.

7. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the amino acid sequences of the variable domains of the first antigen binding site comprise:

SEQ ID NO: 7 for the heavy-chain variable domain (V_H); and
SEQ ID NO: 8 for the light-chain variable domain (V_L).

8. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the nucleotide sequences of the complementarity determining regions (CDRs) of the first antigen binding site comprise:

SEQ ID NO: 9 for CDRH1;

SEQ ID NO: 10 for CDRH2;

SEQ ID NO: 11 for CDRH3;

SEQ ID NO: 12 for CDRL1;

SEQ ID NO: 13 for CDRL2; and

SEQ ID NO: 14 for CDRL3.

9. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the nucleotide sequences of the variable domains of the first antigen binding site comprise:

SEQ ID NO: 15 for the heavy-chain variable domain (V_H); and

SEQ ID NO: 16 for the light-chain variable domain (V_L).

10. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the amino acid sequences of the complementarity determining regions (CDRs) of the first antigen binding site comprise:

SEQ ID NO: 1 for CDRH1;

SEQ ID NO: 21 for CDRH2;

SEQ ID NO: 3 for CDRH3;

SEQ ID NO: 4 for CDRL1;

SEQ ID NO: 5 for CDRL2; and

SEQ ID NO: 6 for CDRL3.

11. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the amino acid sequences of the variable domains of the first antigen binding site comprise:

SEQ ID NO: 22 for the heavy-chain variable domain (V_H); and

SEQ ID NO: 23 for the light-chain variable domain (V_L).

12. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the nucleotide sequences of the complementarity determining regions (CDRs) of the first antigen binding site comprise:

SEQ ID NO: 9 for CDRH1;

SEQ ID NO: 24 for CDRH2;

SEQ ID NO: 11 for CDRH3;

SEQ ID NO: 12 for CDRL1;

SEQ ID NO: 13 for CDRL2; and

SEQ ID NO: 14 for CDRL3.

13. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the nucleotide sequences of the variable domains of the first antigen binding site comprise:

SEQ ID NO: 25 for the heavy-chain variable domain (V_H); and

SEQ ID NO: 26 for the light-chain variable domain (V_L).

14. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the first antigen binding site comprises a set of amino acid sequences at CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, the set selected from the group consisting of the set of SEQ ID NOS:53, 54, 55, 65, 66, and 67, the set of SEQ ID NOS:56, 57, 58, 65, 66 and 67, the set of SEQ ID NOS:59, 60, 61, 65, 66, and 67, and the set of SEQ ID NOS:62, 63, 64, 68, 69 and 70.

15. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the first binding domain comprises a pair of V_H and V_L domains, the pairs selected from the group consisting of SEQ ID NOS:72 and 74, SEQ ID NOS:76 and 78, SEQ ID NOS:76 and 81, and SEQ ID NOS:83 and 85.

16. The antibody of Claim 3 wherein the first VEGF receptor is KDR and the first antigen binding site comprises the set of amino acid sequences CDH1, CDRH2, and CDRH3 given by SEQ ID NOS: 65, 66, and 67, respectively, and a set of amino acid sequences at CDRL1, CDRL2, CDRL3 selected from the group consisting of the set of SEQ ID NOS:106,

107, and 108, the set of SEQ ID NOS:109, 110, and 111, the set of SEQ ID NOS:112, 113, and 114, the set of SEQ ID NOS:115, 116, and 117, the set of SEQ ID NOS:118, 119, and 120, the set of SEQ ID NOS:121, 122, and 123, the set of SEQ ID NOS:124, 125, and 126, the set of SEQ ID NOS:127, 128, and 129, the set of SEQ ID NOS:130, 131, and 132, and the set of SEQ ID NOS:133, 134, and 135.

17. The antibody of Claim 3 wherein the first VEGF receptor is KDR, the V_H domain of first binding domain comprises SEQ ID NO:76, and the V_L domain of the first binding domain comprises a sequence selected from the group consisting of SEQ ID NO:87, SEQ ID NO:89, SEQ ID NO:91, SEQ ID NO:93, SEQ ID NO:95, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, and SEQ ID NO:105.

18. The antibody of any one of Claims 6 to 17 wherein the second VEGF receptor is Flt-1 and the second antigen binding site comprises the heavy chain and light chain variable domains of Mab 6.12 (ATCC No. PTA-3344).

19. The antibody of Claim 3 wherein the first VEGF receptor is Flt-1 and the amino acid sequences of the complementarity determining regions (CDRs) of the first antigen binding site comprise:

SEQ ID NO: 35 at CDRH1;
SEQ ID NO: 36 at CDRH2;
SEQ ID NO: 37 at CDRH3;
SEQ ID NO: 38 at CDRL1;
SEQ ID NO: 39 at CDRL2; and
SEQ ID NO: 40 at CDRL3.

20. The antibody of Claim 3 wherein the first VEGF receptor is Flt-1 and the amino acid sequences of the variable domains of the first antigen binding site comprise:

SEQ ID NO: 41 for the heavy-chain variable domain (V_H); and
SEQ ID NO: 42 for the light-chain variable domain (V_L).

21. The antibody of Claim 3 wherein the first VEGF receptor is Flt-1 and the nucleotide sequences of the complementarity determining regions (CDRs) of the first antigen binding site comprise:

SEQ ID NO: 43 for CDRH1;

SEQ ID NO: 44 for CDRH2;

SEQ ID NO: 45 for CDRH3;

SEQ ID NO: 46 for CDRL1;

SEQ ID NO: 47 for CDRL2; and

SEQ ID NO: 48 for CDRL3.

22. The antibody of Claim 3 wherein the first VEGF receptor is Flt-1 and the nucleotide sequences of the variable domains of the first antigen binding site comprise:

SEQ ID NO: 49 for the heavy-chain variable domain (V_H); and

SEQ ID NO: 50 for the light-chain variable domain (V_L).

23. The antibody of Claim 3 wherein the first VEGF receptor is Flt-1 and the first antigen binding site comprises the heavy chain and light chain variable domains of Mab 6.12 (ATCC No. PTA-3344).

24. An antibody that binds specifically to an extracellular domain of a first VEGF receptor and an extracellular domain of a second VEGF receptor, wherein binding of the antibody to the first or the second VEGF receptor neutralizes activation of that VEGF receptor.

25. The antibody of Claim 24 which blocks binding of VEGF.

26. The antibody of Claim 24 which blocks receptor homodimerization.

27. The antibody of Claim 24 which blocks receptor heterodimerization.

28. The antibody of Claim 24 wherein the first and second VEGF receptors are selected from the group consisting of KDR, Flt-1 and Flt-4.

29. The antibody of Claim 24 wherein the first VEGR receptor is KDR and the second VEGR receptor is Flt-1.

30. An antibody that binds specifically to an extracellular domain of a first VEGF receptor and an extracellular domain of a second VEGF receptor and reduces tumor growth.

31. The antibody of Claim 29 wherein the first and second VEGF receptors are selected from the group consisting of KDR, Flt-1 and Flt-4.

32. The antibody of Claim 29 wherein the first VEGR receptor is KDR and the second VEGR receptor is Flt-1.

33. A antibody that binds specifically to an extracellular domain of a first VEGF receptor and an extracellular domain of a second VEGF receptor and inhibits angiogenesis.

34. The antibody of Claim 32 wherein the first and second VEGF receptors are selected from the group consisting of KDR, Flt-1 and Flt-4.

35. The antibody of Claim 32 wherein the first VEGR receptor is KDR and the second VEGR receptor is Flt-1.

36. A method for making an antibody having a first antigen binding site comprising a first immunoglobulin heavy chain variable domain and a first immunoglobulin light chain variable domain that specifically binds to an extracellular domain of a first VEGF receptor, and a second antigen binding site comprising a second immunoglobulin heavy chain variable domain and a second immunoglobulin light chain variable domain that specifically binds to an extracellular domain of a second VEGF receptor, which comprises

a) coexpressing in a host cell

a recombinant DNA construct encoding a first polypeptide having the first immunoglobulin heavy chain variable domain located to the N terminus of the second immunoglobulin light chain variable domain, and

a recombinant DNA construct encoding a second polypeptide having the second immunoglobulin heavy chain variable domain located to the N terminus of the first immunoglobulin light chain variable domain,

for a time and in a manner sufficient to allow expression of the polypeptides and formation of the antibody; and

b) recovering the antibody.

37. The method of Claim 35 wherein the constructs are on the same DNA expression vector.

38. The method of Claim 35 wherein the constructs are on different DNA expression vectors.

39. The method of Claim 35 wherein the host cell is a bacterial cell, a yeast cell or a mammalian cell.

40. The method of Claim 35 wherein the antibody is secreted from the host cell.

41. A method for neutralizing activation of a first VEGF receptor and a second VEGF receptor in a cell which comprises treating a cell with an antibody having a first antigen binding site specific for the first VEGF receptor and a second binding site specific for the second VEGF receptor in an amount sufficient to neutralize activation of the receptors.

42. A method for reducing tumor growth in a mammal in need thereof comprising treating the mammal with an antibody having a first antigen binding site specific for the first VEGF receptor and a second binding site specific for the second VEGF receptor in an amount effective to reduce tumor growth.

43. A method for inhibiting angiogenesis in a mammal in need thereof comprising treating the mammal with a bispecific antibody having a first antigen binding site specific for the first VEGF receptor and a second binding site specific for the second VEGF receptor in an amount effective to inhibit angiogenesis.